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| EXAMINER | |
|---|---|
| ARIANI, KADE | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/538,767 | MEGENEY ET AL. | |
| | Examiner | Art Unit | |
| | Kade Ariani | 1651 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) 1-22 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-22 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## *DETAILED ACTION*

Claims 1-22 are pending in this application and were examined on their merits.

### *Claim Rejections - 35 USC § 101*

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 3 -11 provide for the use of a caspase-3 protein, but, since the claims do not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 3 -11 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12-15, and 17-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting the differentiation of myoblast and striatal stem cells, with z-DEVD-FMK, a pharmacological inhibitor of caspase-3 activity, *in vitro* or in cell culture, does not reasonably provide enablement for any population of stem cells (cardiac, cortical, bone marrow, etc.), any modulator, any modulator that increases the activity of caspase-3 and induce stem cell differentiation, and also for the method to be performed *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described by the court *in In re Wands*, 8 USPQd 1400 (CA FC 1988). Wands states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

**The nature of the invention**

The claims are drawn to a method of modulating stem cell differentiation. The invention is in a class of invention, which CAFC has characterized as "the unpredictable arts such as chemistry and biology." Micogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed Cir. 2001).

**The breadth of the claims**

The claims broadly encompass any stem cell, any modulator, and experiments *in vivo, ex vivo,* or *in vitro.*

**Quantity of Experimentation**

The quantity of experimentation in this area is extremely large since there is a significant number of modulators and types of stem cells that need to be examined. It would require significant study to identify modulators of stem cell differentiation as well as their actual functions. This would require years of inventive effort, with each of the many inventing steps, not providing any guarantee of success in the succeeding steps.

The unpredictability of the art and the state of the prior art

The art is unpredictable with regard to modulators of stem cell differentiation.

Banks et al. (BLOOD, 2000, Vol. 96, No.12, p.4002) discloses survivin did not affect caspase-3 activity, Callus & Vaux (Cell Death and Differentiation, 2007, Vol. 14, p.73-78) discloses cIAP1 and cIAP2 do not directly inhibit caspases at physiological concentrations (Table.1, p.74).

S. Kumar in a review article recites, "Unresolved issues and controversies in caspase biology, including, how some caspases can function in both apoptotic and nonapoptotic pathways (differentiation) and factors that regulate the alternative caspase function and what pathways of caspase activation exist in the absence of initiator caspases..." (Cell Death & Differentiation, 2007, Vol.14, p.40, Col.2, last paragraph).

## Working examples

In the specification, the working examples are drawn to inhibition of caspase-3 activity by z-DEVD-FMK in cell culture of myoblast and striatal stem cells.

Guidance in the Specification

The specification does teach how to use this method for any population of stem cells (cardiac, cortical, bone marrow, etc.), any modulator, any modulator that increases the activity of caspase-3 and induce stem cell differentiation, and also for the method to be performed *in vivo*.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

Thus given the broad claims, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the presence of only two working examples and the negative teachings of the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written and the instant application does not support the breadth of the claims.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-6, 8-15, and 17-21 are rejected under 35 U.S.C. 102(a) as being anticipated by Fernando et al. (PNAS, August 2002, Vol.99, p. 11025-11030).

Claims 1-6, 8-15, and 17-21 are drawn to a method of screening for compounds that modulate stem cell differentiation comprising identifying a modulator of caspase-3

activity by contacting a caspase-3 protein with a candidate compound, measuring the activity of the caspase-3 protein and comparing the measured activity with the activity of caspase-3 protein in the absence of the candidate, a method of modulating stem cell differentiation comprising contacting a stem cell, or a population of stem cells, with one or more modulators of caspase-3 activity, wherein said one or more modulators are selected from the group of pro-caspase 3, active-caspase 3, Mammalian Sterile Twenty-like kinase 1 (MST1), MEKK1, ASK1, SLK, MKK6, MKK3, p38α, p38γ, XIAP, c-IAP2, c-IAP1, survivin, caspase-1, caspase-8, caspase-9, caspase-10, Granzyme B, I- FLICE and CrmA, or a combination thereof, wherein said one or more modulators attenuate the activity of caspase-3 and inhibit stem cell differentiation, wherein said stem cell, or population of stem cells comprise muscle stem cells, cardiac stem cells, neural stem cells, cortical stem cells, bone marrow stem cells or a combination thereof, wherein said stem cell, or population of stem cells, wherein said stem cell, or population of stem cells are *ex vivo,* wherein said stem cell, or population of stem cells are *in vitro*, and a method wherein said stem cell, or population of stem cells, are contacted sequentially with a modulator that attenuates the activity of caspase-3 and inhibits stem cell differentiation and a modulator that increase the activity of caspase-3 and induces stem cell differentiation..

Fernando et al. disclose a method of screening for compounds that modulate stem cell differentiation comprising identifying a modulator of caspase-3 activity by contacting a caspase-3 protein with a candidate compound, measuring the activity of

the caspase-3 protein and comparing the measured activity with the activity of caspase-3 protein in the absence of the candidate ( Material & methods), a method wherein stem cell differentiation is modulated by a modulator of caspase-3 activity (see p. 11025, Col. 2, Last paragraph, also Fig. 2, p.11027), myoblast cultures were treated with.... (Material & Method, p. 11025-26), caspase 3-inhibited myoblasts displayed an impaired formation of myotubes (p. 11028, second paragraph, Lines 4-5), caspase-3 activates MST1 kinase during differentiation and an *in vitro* assay (p. 11028, Col. 2, Line 6 and p. 11029, Col.1, Lines 24-25), contacting cells with MST1 (activator of caspase-3) after z-DEVD.fmk (inhibitor of caspase-3) treatment (p.11027, Col.1, Lines 3-5), and further disclose, "similar signaling components (MST1, MKK6, p38) are also found in numerous differentiated cell types including. ...Neurons... and it is reasonable to suggest that caspase 3/MST1 signaling may be an indispensable component for cellular differentiation in general" (p. 11030, Lines 7-12).

Fernando et al. therefore clearly anticipates the claimed invention.

It has been noted that Fernando et al. do not explicitly state a method wherein stem cells are *ex vivo*. However according to on line "Stedman's medical dictionary 27th edition" the definition of *ex vivo* is the use or positioning of a tissue or cell after removal from an organism while the tissue or cells remain viable, therefore, Fernando et al. cell culture can be considered *ex vivo*.

Claims 1-8, 10-17, and 19-20 are rejected under 35 U.S.C. 102(b) as being anticipated by Zermati et al. (J. Exp. Med., 2001, Vol. 193, p. 247-254).

Zermati et al. disclose a method of screening and a method of modulating stem cell differentiation by contacting with a modulator of caspase 3 activity (p. 249, Col. 1, 2nd paragraph and Fig. 2), initiator caspases such as caspase –2, -8, and –9, pro-forms of effector caspases e.g. caspase-3, control activation of the former caspase enzymes (p. 250, Col. 1, 2nd paragraph, Lines 5-6), *in vitro* (p. 251, Col 1, 2nd paragraph, Line 15), Zermati et al further discloses these observations suggested that caspase activation was required for maturation after the stage of differentiation (p.249, Col. 2, lines 5-7).

It has been noted that Zermati et al. do not explicitly state a method wherein stem cells are *ex vivo*. However according to "online Stedman's medical dictionary 27th edition" the definition of *ex vivo* is the use or positioning of a tissue or cell after removal from an organism while the tissue or cells remain viable, therefore, Zermati et al. cell culture can be considered *ex vivo*.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zermati et al. (J. Exp. Med., 2001, Vol. 193, p. 247-254) in view of Kuida et al. (Nature,

1996, Vol. 384, p.368-372), and further in view of Jeon et al. (J. Neurochem. 1999, Vol. 73, No. 1, p. 322-333).

As discussed immediately above, Zermati et al. teach the limitations of claims 1-8, 10-17, and 19-20. Zermati et al. do not teach stem cells are *in vivo*, and formulating a compound that modulates stem cell differentiation into a pharmaceutically acceptable form. However, Kuida et al. teach a method of analyzing the function of caspase-3 (CPP32/yama/apopain) during brain development of CPP32-deficient mice *in vivo* and its critical role during differentiation of cells and tissues in the early embryo (p. 384, abstract), Kuida et al. further provides evidence that caspase-3 (CPP32) plays an important role in early development of central nervous system (p.371, Col.2, 2nd paragraph, Lines 27-30).

Moreover, at the time the invention was made, the involvement of the members of caspase family especially caspase-3 in many degenerative disease such as acute and chronic degenerative neurologic disease, was very well known in the art (Jeon et al. see Abstract & Introduction). Thus, one would have been motivated to formulate a modulator of caspase-3 activity into a pharmaceutically acceptable from.

Therefore, in view of the above teachings, it would have been obvious to one of ordinary skill in the art to use the methods of Fernando et al. and Zermati et al. and to provide a method of screening for compounds that modulate caspase-3 activity and a method of modulating stem cell differentiation comprising contacting a population of stem cells with one or more modulators of caspase-3 activity.

***Conclusion***

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kade Ariani whose telephone number is (571) 272-6083. The examiner can normally be reached on 9:00 am to 5:30 pm EST Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on (571) 272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Kade Ariani
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Art Unit 1651

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